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Molecular architecture of the PTG/PP1 holoenzyme

Lafora disease (LD) is a rare, genetic, neurodegenerative disorder manifested by severe teenage onset of progressive myoclonus epilepsy. The patients usually die within 10 years of first symptoms occurrence. There is no cure available. LD is caused by mutations in laforin-malin complex which leads to appearance of neurotoxic inclusion bodies formed by insoluble polyglucosans called Lafora Bodies (LB) [1,2]. One of the key regulatory enzymes in glycogen metabolism is PP1 (type 1 protein phosphatase) which "switches" on or off glycogen synthase and phosphorylase responsible for glycogen synthesis and degradation. PP1 is involved in many cellular processes and acquires its specificity by forming holoenzymes with scaffolding proteins. In neurons PTG (protein targeting to glycogen) binds to PP1 and brings it to its substrates. In healthy neurons PTG is downregulated by laforin-malin complex, mutations in any of these proteins causes accumulation of PTG, which promotes glycogen synthesis by directing PP1 to glycogen synthase and glycogen phosphorylase. In LD mice models knocking out PTG resulted in a nearly complete disappearance of LB and resolution of neurodegeneration and myoclonic epilepsy, indicating that small molecules interfering with the PTG/PP1 interaction emerges as a promising therapeutic strategy for LD [3,4,5]. Up to date, there was no structural data of PTG and PTG/PP1 complex allowing for identification of potential druggable pockets. We present our efforts to obtain structural information of PTG-CBM21 and PTG/PP1 complex. Herein we report the first structures of human PTG: PTG-CBM21 in complex with β-cyclodextrin, PP1 in complex with PTG N-terminal peptide containing the conserved binding motif RVXF and finally PTG/PP1 holoenzyme.
Our findings contribute to elucidating the interplay mechanism between PTG and PP1 and provide the basis for further structural analysis in order to identify druggable pocket.

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